UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,471	10/25/2001	Mehran M. Khodadoust	50200/002003	6131

21559 7590 05/15/2006

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,471	KHODADOUST, MEHRAN M.	
	Examiner	Art Unit	
	Michele K. Joike, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed February 23, 2006. Claims 1-82 were canceled. Claims 83-109 were added.

Claims 83-109 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed October 21, 2005, that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action and/or sets forth new rejections that are necessitated by amendment, this Office Action is made FINAL.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 83, 84, 88-96, 98-104 and 107-108 are rejected under 35 U.S.C. 102(b) as being anticipated by Baetscher et al (U.S. 5,922,601).

Although these are new claims, the 102 (b) rejection made against claims 53, 56, 57, 59, 60, 63-68 and 79-82, as being anticipated by Baetscher et al in the previous office action applies here because the new claims comprise the same limitations as the cancelled claims.

The following rejections are based on the following interpretation of the term "reporter." Absent an explicit definition to the contrary, a "reporter" is any polypeptide sequence (as encoded by a polynucleotide sequence) that can be detected by conventional means. This includes colorimetric assays, bio- or chemiluminescence assays, as well as screening assays such as selection on a particular growth medium (such as a positive or negative selection marker). Because any polypeptide sequence can be detected by some means (e.g., by measuring its enzymatic activity, or detecting it with specific antibodies), any polypeptide meets the limitation of being a "reporter."

To reiterate the rejection:

Baetscher et al teach a gene trap nucleic acid construct comprising the following elements in a 5'-to-3' orientation:

Splice acceptor---IRES---Neo-HSV-TK (see for example Figure 2).

Because the Neomycin resistance gene is a positive selection marker and HSV-TK is a negative selection marker the above specific construct teaches the following general formula:

Splice acceptor---IRES---positive selection---negative selection.

This nucleic acid construct is then placed within the context of a retroviral vector construct (see for example column 12, lines 34-55), which along with LTR elements (i.e., integration sequences) additionally contains selectable or assayable markers, including those useful in "fluorescence activated cell sorting" (see for example column 8, lines 50-57). Thus, the general formula of the nucleic acid construct taught by Baetscher et al has the overall general formula of:

Splice acceptor---IRES---positive selection---negative selection---reporter.

In order to get expression of the reporter, a promoter element must be operatively linked to the reporter gene. Thus, the construct taught by Baetscher et al can further be visualized as having the following general formula:

Splice acceptor---IRES---positive selection---negative selection---STOP---Promoter---reporter.

Importantly, as set forth above, the retroviral vector further comprises selectable or assayable markers, including those useful in "fluorescence activated cell sorting" (see for example column 8, lines 50-57). Such a reporter can be a "protein that spontaneously emits light...Green Fluorescent Protein (GFP)" (see for example column 10, lines 12-19).

Notably, the Neo-HSV-Tk marker is not operably linked to a promoter within the context of the nucleotide construct; i.e., it is a promoterless marker construct (see for example column 5, lines 44-67). As a result, the selection markers are only expressed when the construct integrates into the genome of a host cell, and the selection markers become operably linked to an endogenous promoter element of the host cell (see for example column 13, lines 25-33). Thus, Baetscher et al also teach a host cell comprising the claimed nucleic acid constructs/vectors.

Finally, Baetscher et al teach a particular vector having the following formula:

Splice acceptor---IRES---Neo-HSV-TK---STOP---Promoter---Ampicillin.

Support for such a vector comes both from the above analysis of the teachings, and from column 12, lines 63-67, which indicate that the retroviral vector of the element

can contain "regulatory elements suitable for propagation and selection in *E. coli*." This includes the Ampicillin resistance gene, which can serve as a positive selection marker (in the presence of ampicillin), and a prokaryotic promoter (i.e., regulatory element) to allow the expression of the Ampicillin resistance gene. Furthermore, given the interpretation of a reporter molecule set forth above, the Neomycin resistance gene can also be a reporter, allowing for the following formula:

Splice acceptor---IRES---reporter---negative marker---STOP---Promoter---positive marker.

In conclusion, Baetscher et al meets all of the limitations of the newly added claims, and therefore anticipates the claimed invention.

Response to Arguments Concerning Claim Rejections – 35 USC § 102 (b)

Applicant's arguments filed February 23, 2006 have been fully considered but they are not persuasive.

The following grounds of traversal are presented:

1) Claims 83, 84 and 85 include the new limitation that the negative selection marker, positive selection marker and reporter gene are all operably linked to regulatory elements of a host cellular gene after the nucleic acid is contacted with a cell, and Baetscher et al do not disclose this limitation.

2) Claims 88-91 and 92-96 are dependent on claims containing the limitation as described above, so also should be allowable.

3) Claims 86, 97 and 109 have a transactivator incorporated in the nucleic acid cassette or vector, which Baetscher et al do not teach.

Applicant's first and second arguments have not been found persuasive for the following reasons.

Claim 83, dependent claims 84 and 85, comprise a nucleic acid including a splice acceptor site and a cassette including a negative selection marker, a positive selection marker and a reporter gene operably linked to regulatory elements of a host cellular gene. "Operably linked" is defined by the specification as "nucleotide sequences which are linked, whether to encode an mRNA transcript of a desired gene product, or for regulatory control. 'Operably linked' can also mean that selectable marker, transactivator, and reporter genes are encoded by the same transcription unit." (p. 32, lines 24-27). Therefore, Baetscher et al who teach, splice acceptor site---IRES---positive selection---negative selection---reporter, all under the same endogenous promoter of "a host cellular gene", still anticipates claim 83, because the same transcription unit can be used for the selection markers and the reporter gene.

Claims 88-96 are dependent on claims 83, 84 or 86. Since Baetscher et al disclose the limitations set forth in claim 83 as described above, which is rejected as being anticipated by Baetscher et al, the argument that these claims are now allowable as being dependent from an allowable claim is moot. Also, as reiterated above, claims 88-96 are anticipated by Baetscher et al as well.

Regarding claims 86, 97 and 109, Applicant's traversal has been fully considered and found to be persuasive in that Baetscher at al does not teach a transactivator

incorporated in the nucleic acid cassette or vector. The 35 USC §102(b) rejection is withdrawn for claims 86, 97 and 109. However, applicant's amendment has necessitated the new grounds of rejection under 35 U.S.C. 103(a) recited below.

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 85 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baetscher et al in view of MPEP § 2144.04 (VI)(C).

Although this is a new claim, the 103 (a) rejection made against claims 54 and 55, as being anticipated by Baetscher et al in view of MPEP § 2144.04 (VI)(C) in the previous office action apply here because the new claim comprises the same limitations as the cancelled claims.

To reiterate the rejection:

Baetscher et al teach all of the elements set forth above in the rejection under 35 USC § 102(b); this includes all of the specific elements set forth as limitations in each embodiment of the instant claims. However, Baetscher et al do not specifically teach the different orientations as set forth in each embodiment of the claims. Although Baetscher et al teach the presence of each element set forth in claim 85, they do not set forth the specific order. It is simply that a different order of the elements is used.

MPEP § 2144.04 (VI)(C) cites that the rearrangement of parts is an obvious matter of design choice, unless the variation modifies the operation of the device. In the instant case, the particular elements set forth in the claimed nucleic acids are not indicated as altering the function of the claimed nucleic acids based upon their positioning. Indeed, the specification teaches that each nucleic acid is to be used for the same function, the generation of a library of cells under the control of specific regulatory elements (see pages 5-6 of the instant specification). Because each of the nucleic acids set forth in the claims have the same elements and the same function, it would be obvious for the ordinary skilled artisan to alter the sequence of the elements within the nucleic acids as a matter of design choice. This is merely an aesthetic choice, and confers no patentable functional distinction on the vectors (based on the instant disclosure). The ordinary skilled artisan would have been motivated to alter the sequence of the elements within the nucleic acids because the function of each element is the same as in the particular orientation taught by Baetscher et al, and such rearrangements have been determined to be patentably equivalent. Absent evidence to the contrary (i.e., some teaching in the instant specification indicating that each particular order of elements confers a patentably distinct function on the claimed nucleic acids), the ordinary skilled artisan would have had a reasonable expectation of success when altering the order of the elements taught by Baetscher et al to arrive at each of the claimed embodiments of the invention.

Claims 87 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baetscher et al in view of Zambrowicz *et al.* (US 6,436,707; see entire document.)

Although these are new claims, the 103 (a) rejection made against claims 56, 58 and 61 as being anticipated by Baetscher et al in view of Zambrowicz et al in the previous office action apply here because the new claims comprise the same limitations as the cancelled claims.

To reiterate the rejection:

Baetscher et al teach all of the elements set forth above. Briefly, Baetscher teaches the construction of gene trap vectors comprising a splice acceptor site, positive/negative selection markers, IRES elements, Stop codons, polyadenylation sequences and reporter genes, in various orders. However, Baetscher et al do not teach the specific use of recombinase sequences in their nucleic acids.

Zambrowicz et al teach the construction of gene trap vectors (see for example the Abstract, column 2, lines 10-31), comprising many of the elements set forth in the teachings of Baetscher et al such as splice acceptor sites, IRES elements and positive/negative selectable marker genes. Zambrowicz et al also teach the use of recombinase sites within the gene trap cassette (see for example column 8, lines 40-55), and indicates that these sites have the advantage of allowing the conditional activation or deactivation of the gene trap (see for example column 10, lines 22-30). It would have been obvious for the ordinary skilled artisan to combine the teachings of Baetscher et al and Zambrowicz et al to arrive at the instantly claimed nucleic acids because the teachings both concern the making and using of gene trap vectors, and

thus are clearly combinable. The ordinary skilled artisan would have been motivated to combine the teachings of Baetscher et al and Zambrowicz et al to utilize recombinase sites because Zambrowicz et al clearly teach the advantage of being able to turn on and off the gene trap mechanism using said sites. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when combining the teachings of Baetscher et al and Zambrowicz et al.

Claims 86, 97, 105 and 109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baetscher et al in view of Massie et al. This is a new rejection necessitated by amendment.

Baetscher et al teach all of the elements set forth above. Briefly, Baetscher et al teach the construction of gene trap vectors comprising a splice acceptor site, positive/negative selection markers, IRES elements, Stop codons, polyadenylation sequences and reporter genes, in various orders. However, Baetscher et al do not teach a transactivator incorporated into a cassette or vector, specifically, they do not teach the transactivator being a tetracycline regulator (tTA).

Massie et al (J. of Virology, 72 (3): 2289-2296, 1998, specifically p. 2289, Materials & Methods and 2295) teach a cassette and then a vector comprising the tTA transactivator.

The ordinary skilled artisan, desiring to use a cassette or vector with a splice acceptor site, positive/negative selection markers, a reporter gene and a tTA transactivator, would have been motivated to combine the teachings of Baetscher et al

teaching the construction of gene trap vectors comprising a splice acceptor site, positive/negative selection markers, IRES elements, Stop codons, polyadenylation sequences and reporter genes, in various orders, with the teachings of Massie et al, teaching a cassette and then a vector comprising the tTA transactivator, since a vector with tTA in it is useful for functional studies and gene therapy applications. It would have been obvious to one of ordinary skill in the art to incorporate tTA into the vector because the tTA system has been shown to be highly effective for the regulated expression of recombinant proteins. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Arguments Concerning Claim Rejections – 35 USC § 103 (a)

Applicant's arguments filed February 23, 2006 have been fully considered but they are not persuasive.

The following grounds of traversal are presented:

1) Applicant argues that the cancellation and substitution of new claims comprise limitations not taught by Baetscher et al, regardless of order of orientation, therefore MPEP § 2144.04 (VI)(C) does not apply.

2) Baetscher et al do not teach all of the limitations of the claims, and Zambrowicz et al fail to cure the deficiencies.

Applicant's arguments have not been found persuasive for the following reasons.

Baetscher et al teach all the limitations of claims 83, 84, 88-96, 98-104 and 107-108, as described above. MPEP § 2144.04 (VI)(C) does apply to claim 85 when combined with Baetscher et al, also as described above. Zambrowicz et al do not need to cure the deficiencies of Baetscher et al, since Baetscher et al have no deficiencies regarding claims 83, 84, 88-96, 98-104 and 107-108, nor when combined with Zambrowicz et al for claims 87 and 106.

Allowable Subject Matter

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike, Ph.D. whose telephone number is 571-272-5915. The examiner can normally be reached on M-F, 9:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele K Joike, Ph.D.
Examiner
Art Unit 1636